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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,868	07/10/2003	Dominique Rigal	8076.294USW1	1456

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,868	RIGAL ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 18-32* is/are pending in the application.

4a) Of the above claim(s) *2,4,5,18-20 and 23-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3,6-10,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-10 and 18-32 are pending. Claims 11-17 were cancelled in the Preliminary Amendment, filed 1/26/04.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1, 3, 6-10, 21 and 22, in the reply filed on 4/19/06 is acknowledged. The traversal is on the ground(s) that a search of groups II and III in addition to group I would not be burdensome. This is not found persuasive because the search of the different groups would be considered a search burden because the search strategy would be different even though some of them are classified together. Because of the significant reliance upon the non-patent literature in examination of the biotechnology art, applications are rarely searched by classification and are more commonly search by terminology, therefore search burden is based upon additional or different terms that must be added to the search query. In the instant case, additional terms such as CD40, CD83, CD86, HLA-DR, CD14, CD1a, various antigens, antigen presentation, non-covalent bond to RU 41740 or analogue, etc...would need to be search in several different databases, therefore resulting in multiple additional searches. Examiner agrees that some of these CD markers will be present in the art of Group I, however, there is even an additional search burden in searching for the claimed profile of expression of these markers. This level of additional search is consider undue and would be considered a search burden for the Office.

Claims 2, 4, 5, 18-20, and 23-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/19/06.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 3, 6-10, 21 and 22 are under consideration.

Priority

3. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Although priority papers have been submitted in the instant case, a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Therefore, the teachings of XXX et al. are applicable against the instant claims.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted was filed on 1/26/04. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: The description of Figure 4 includes A-D labels not present in the drawings. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

6. The disclosure is objected to because of the following informalities: A typographical error reciting "the_ingivitis_tion" is present on page 2, line 1 of the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

7. Claims 1, 3, 8, 9, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a method for obtaining mature dendritic cells or activated macrophages from monocytes (Mon), monocyte precursors (MonP), or hematopoietic stem cells (HSC) comprising contacting said Mon, MonP, or HSC with RU41740 or an analogue thereof wherein said contacting results in maturation of Mon, MonP, or HSC into mature dendritic cells.

When the claims are analyzed in light of the specification, the instant invention encompasses any RU41740 analogue. However, the specification discloses only LCOS 13 and LCOS14. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. While the specification discloses, in general terms, the genus RU 41740, LCOS 13 and LCOS14 (p.6, lines 17-30). Considering that RU 41740 is a non-specific glycoprotein extract, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises any RU 41740 analogue.

Next, then it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The specification discloses generally broadly defines an RU 41740 analogue as a compound consisting of glycoprotein extracts obtained a *Klebsiella* strain as a result of at least the following steps: culture of the strain, lysis of the bacterial cells walls organic extraction, centrifugation, ultrafiltration, drying (p. 5, lines 26-33 to p. 6, line 1). In example 10 (p. 28-35), the specification provides a method of extracting LCOS13 from strain of *Klebsiella pneumonaie.* In example 11 (p. 35-38), the culture of monocytes in the presence of LCOS13 cause monocytes maturation to a dendritic phenotype (Tables on page 37) and demonstrate high allostimulatory capacity and stimulate autologous T lymphocytes (p. 38 par 1 and 2). This description does not specify a strange nor the components of the glycoprotein extract that are necessary to achieve the physiological responses of LCOS13. LCOS14 was not described or listed in the specification as an examples of an RU 41740 analogue.

In conclusion, given the breadth of the genus, RU 41740 analogue, and the limited number of examples provided, and given that breadth of the identifying features/characteristic of a glycoprotein extract from *Klebsiella* strain, the written description requirement disclosing the complete structure of any RU 41740 analogue has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus, RU 41740, at the time the application was filed.

Scope of Enablement

8. Claims 1, 3, 6-10, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining mature dendritic cells from Mon or MonP comprising contacting Mon or MonP with RU 41740 or it analogue, LCOS13, wherein said RU41740 or LCOS13 when placed in contact with Mon or MonP induces functional maturation of theses cell to mature dendritic cells, wherein mature dendritic cells trigger a primary response to an infectious or tumor antigen placed in contact with the dendritic cell before or during their culture with T lymphocytes and also induce the proliferation of T lymphocytes in a mixed autologous or mixed allogenic culture, does not reasonably provide enablement for a method of obtaining dendritic cells from HSC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of

working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification provides examples for the generation of both functional and phenotypic dendritic cells from monocytes using RU 41740 and LCOS13 (see example 1, p. 13-19 example 11, p.35-37, and example 12, p. 38-39). Example 2 teaches the treatment of HSC with RU41740. Maturation to a dendritic cell phenotype was determined by assessing marker profiles that would represent dendritic cell presence. The expression profiles of the markers were inconsistent with those expected for dendritic cells. Dendritic cells would have been expected have relatively low levels or decreasing levels of CD14 and relatively high levels of CD86, CD40, and HLA-DR. However, Table 5 (p. 20) demonstrated that the levels of CD14 increased and CD86, CD40, and HLA-DR over time in culture with RU 41740. Similar results were seen in example 3 with cord blood stem cells. These conflicting results bring about questions as to whether the HSC did or can differentiation into mature dendritic cells as claimed. The specification provides no function or structural assays to further demonstrate that HSC can be stimulated to produce dendritic cells. At the time of filing, the art does not teach a method of generating dendritic cell from HSC using RU41740, therefore an

artisan would rely upon the specification doe the teaching of such a method. Considering the art does not teach a method and the method provided by the specification is questionable, an artisan would not know how to use or make the instant invention in a way to generate dendritic cells from HSC.

Also, because it is not clear that RU41740 will stimulate dendritic cells from HSC, it is also not clear that analogues of RU41740 will function in the claimed manner as well. Therefore, and artisan would not know how to generate dendritic cells from HSC using LCOS13 as well. Because LCOS14 was merely stated in the specification as an analogue of RU41740 with out any further description of its use or functionality and also because LCOS14 is not found in the art, an artisan would not know how to use or make the instant invention with LCOS14 as well.

Biological Deposit

9. Claims 3, 8, 9, and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ biological matter, specifically RU 41740 from strain 0_1K_2NCTC 5055 of *Klebsiella pneumoniae*, LCOS13 and LCOS14. Since the biological materials are essential to the claimed invention, they must be obtained by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of

35 U.S.C.§ 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has deposited the biological materials (p.ZZ of the specification), but there is no indication in the specification of public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over her or her signature and registration number, stating that the specific biological have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over her or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained I a public depository for a period of 30 years or 5 years after the last request or the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R.§ 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention id directed to M.P.E.P §2411.05, as well as to 37 C.F.R.§ 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicant is advised that the address for the ATCC has recently been changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 6, 7, 10, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garin et al (In J Immunopharmac 13(1):69-74, 1996; of record) and Brossart et al (Blood 92(11):4238-4247, 1998).

The instant invention is drawn to to a method for obtaining mature dendritic cells or activated macrophages from Mon, MonP, or HSC comprising contacting said Mon, MonP, or HSC with RU41740 or an analogue thereof wherein said contacting results in maturation of Mon, MonP, or HSC into mature dendritic cells by triggering a primary response in vitro against an infectious or tumor antigen placed in contact with the dendritic cell beforehand and/or during their culture with the T lymphocytes; and inducing the proliferation of T lymphocytes in a mixed autologous culture or mixed allogenic culture. Narrowing embodiments specify that RU41740 or RU41740 coupled to antigenic molecules, that the treatment be done ex vivo, and that RU41740 be at a final concentration between 1 ng/ml and 1 mg/ml or 100ng/ml and 50μg/ml.

Brossart et al. teach methods of stimulating Mon or MonP to differentiate in to dendritic cells using IL-4, TNFα, and/ or LPS. They also disclose that culturing monocytes with CD40L alone can also effectively stimulate differentiation of Mon into dendritic cells. The verify the generation of dendritic cells from Mon using functional analysis. For functional analysis , cell were tested for their ability to stimulate alogeneic T lymphocytes in mixed lymphocyte reaction, and to induce primary HIV-peptide-specific cytotoixic T-calls responses in vitro. Cells cultured with CD40L displayed all phenotypic and functional characteristics of mature dendritic cells and were potent simulatory cells in prining of MHC class I –restricted CTL responses against HIV-peptide (See abstract). Brossart et al does not teach the use of RU41740 to generate dendritic cells from Mon, MonP, or HSC.

Garin et al. disclose that RU 41740 possesses immunomodulating properties in monocytes, in part, by improving phagocytic functions (p. 69 par 1). They also demonstrate modulation of markers associated with dendritic cell phenotype and function. They also teach culturing with RU 41740 at a concentration between a range of 100ng/ml and 50μg/ml (Fig 1)or 1 mg/ml (Fig 2 and 3). Because Garin et al and others before them demonstrate immunostimulatory effects in monocytes and artisan would have motivation, as well as being obvious to the methods to verify that the monocytes are being immunostimulated by the standard methods described above in Brossart et al. Garrin et al does not teach the method of assessing functionality of dendritic cells.

The claims also specify that RU 41740 be "coupled to an antigenic molecule". Given the broadest reasonable interpretation "coupled" can encompass co-administration, and therefore the presence of the HIV-peptide antigen in culture with the stimulatory agent taught by Brossart et would encompass this limitation. Furthermore, the claims are drawn to ex vivo treatment. Since the monocytes are isolated from subjects and manipulated in culture in both Brossart et al and Garrin et al. This would encompass ex vivo treatment. The RU 41740 concentrations were limited by the claims. As discussed above, Garrin et al teach some of the concentrations claimed. However, culturing in various concentration of RU4170 would be considered with the realms of standard optimization of a method and therefore obvious to an artisan (MPEP 2144).

Overall, at the time of the invention, it would have been obvious to an artisan of ordinary skill to use the methods of determining functionality of dendritic cell as taught by Brossart et al to further demonstrate the immunostimulatory impact of RU 41740 on monocytes. Garrin et al provide the motivations for the use of these method because they show data suggestive of the generation of dendritic cell phenotypes in the cultured monocytes following culture with RU 41740. Furthermore, it also would have been obvious to an artisan of ordinary skill to combined these methods with a reasonable expectation of success because the method taught by Brossart et al are the standard type of methods to demonstrate immunostimulation of dendritic cells.

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble